

**REMARKS**

Entry of the foregoing, reexamination and reconsideration of the above-identified application is respectfully requested.

Applicants note the indication by the Examiner of duplicate claims. Upon indication of allowable subject matter, duplicate claims will be deleted.

Claims 30, 48-55, 62, 71, 72, 74, 75, 77-91, 96 and 99 have been rejected under 35 U.S.C. § 112, second paragraph, for purportedly being indefinite. This rejection is traversed in part and now moot in part.

Claims 30, 50, 62, 72, 74, 75, 82, 96 and 99 are allegedly vague and unclear due to the term "derivatives." It is respectfully submitted that these claims clears would be sufficiently clear to a person skilled in the art reading the claims in light of the specification.

Under 35 U.S.C. §112, second paragraph, a specification shall include claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Determining whether a claim is indefinite requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification.... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." Credle v. Bond, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994).

Applicants' specification clearly defines the term "derivative," as used in the claims. "Derivatives" as used in claims 30, 50, 72, 74, 7, 82 and 99 is defined in the paragraph bridging pages 4-5 of the specification. The claim encompasses "derivatives [of the thiolated polymer] obtained by auto-cross-linking, introduction of functional groups, attachment of

complexing agents (such as, e.g., EDTA), coupling of enzyme inhibitors, etc., in particular in case of polymers comprising negatively charged groups, e.g. COO<sup>-</sup> groups." With respect to "derivatives" as used in claims 62 and 96, one skilled in the art would recognize that any known cysteine derivative, e.g., homocystein, N-acetylcysteine, cysteinemethylester, could be used in the instant invention. As described in the specification, the important chemical property of the cysteine and cysteine derivative for purposes of the invention is the compound has a functional amino group and is a thiol-containing compound. This would be clear to a person skilled in the art at the very least based on the description at page 9, last paragraph - page 10, second paragraph.

Since the claims when read in light of the specification would be sufficiently clear to a person skilled in the art, withdrawal of the rejection is respectfully requested and believed to be in order.

Claims 48, 50, 53-55, 87 and 89-91 are purportedly vague and unclear due to the phrase "an effective amount." This rejection is believed to be rendered moot by the instant amendment. The claims have been amended to more clearly define for what the amounts are effective. The desired effects are thus now specified in the claims. These are not narrowing amendments since the desired effects were inherent in the recitation of "an effective amount."

In claims 53 and 89, the phrase "a method of treating an individual in need of a treatment" is purportedly not clear. This aspect of the rejection is now moot in view of the amendments to these claims. More specifically, the claims have been amended to recite, a "method of administering an active ingredient to an individual in need thereof wherein the active ingredient is taken up via mucosae . . ." This makes clear that the individual is one in

need of the active ingredient. This amendment is not narrowing since it makes more clear what was implicit in the claim.

Claim 53 was also rejected, because the phrase "the active ingredient" purportedly lacks antecedent basis. The above amendment to claim 53 overcomes this aspect of the rejection.

In claim 71, the phrase "said drug" purportedly lacks antecedent basis. This rejection is now moot in view of the amendment to recite "said pharmaceutical composition." This amendment does not narrow the scope of the claim.

Claim 72 has been amended to correct the typographical error as helpfully noted by the Examiner.

In view of the above, withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claims 1 and 28-32 have been rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by Constancis et al (U.S. Patent No. 5,496,872). This rejection is respectfully traversed.

The Federal Circuit has previously held that prior art is anticipatory only if every element of the claimed invention is disclosed in a single item of prior art in the form literally defined in the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986), *cert denied*, 480 US 947 (1987). This standard is clearly not met in the instant application.

Constancis describes monomer molecules ("oligomers") having SH groups, which upon polymerization by oxidation are formed into disulfide bridges. The polymers resulting

from the polymerization process, however, do not contain any non-terminal thiol groups. The non-terminal thiol groups of the instant invention were found to bind to the glycoproteins in mucus, thus allowing for a stable localization of the polymers on certain mucosae in the mucus. *See, e.g.*, pages 2-3 of the specification.

By contrast with the polymers of Constancis, the claimed invention is directed to a "mucoadhesive polymer comprising not more than 10 different monomers and at least one non-terminal thiol group." Since Constancis' polymers do not contain any non-terminal thiol groups, this reference fails to anticipate or render obvious applicants' invention.

Furthermore, the polymers of Constancis will not be "mucoadhesive" as recited in applicants' claims. Instead, the polymers of Constancis are "bioadhesive." These two classes of compounds are distinct. The compounds used by Constancis may be used *in vitro* or *in vivo* for binding biological tissues to each other or for binding a biological tissue and, e.g., an implanted biomaterial. The mucoadhesive polymers are intended to bind to the mucus gel layer and not to a tissue.

The term "mucoadhesive" in the preamble must be considered in evaluating the claims. Limitations in the preamble are considered where such limitations are necessary to give meaning to the claim and properly define the invention. *Perkin Elmer Corporation v. Computervision Corporation*, 221 USPQ 669, 675 (Fed. Cir. 1984). Mucoadhesive polymers have particular properties, which differ from those of bioadhesives. Mucus is a loosened, extremely wide meshed network which is characteristic for the mucus layers. Unlike for bioadhesives, a tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is neither necessary nor desired for a mucoadhesive polymer. A covalent binding of the

mucoadhesive polymer directly to the tissue surface could have extremely negative effects. Mucoadhesive polymers thus should specifically bind to the mucus layer above the tissue in these areas. With a mucus turnover of about 6-8 hours, adverse effects obtained by binding are prevented by covalently linking the mucoadhesive polymers to the mucus rather than the tissue itself. *See, e.g.*, page 2, first paragraph.

In failing to describe mucoadhesive polymers having non-terminal thiol groups, Constancis fails to describe or render obvious applicants' claimed invention. Withdrawal of the rejection under §102(b) is thus respectfully requested and believed to be in order.

Claims 1 and 28-99 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Bernkop-Schnurch et al (*Intl. J. Pharm.* 157:17-25 (1997) and *Intl. J. Pharm.* 146:247-254 (1997)) in view of Constancis et al (U.S. Patent No. 5,646,239). This rejection is respectfully traversed.

As noted by the Examiner, Bernkop-Schnurch discloses mucoadhesive polymers, however, fails to disclose polymers having thiol groups as in the instant invention. Constancis is cited for its teaching of modification of biomaterials with thiolated compounds. However, as noted above, Constancis fails to disclose or even suggest mucoadhesive polymers having at least one non-terminal thiol group. Constancis instead discloses bioadhesive substances having polysulfide crosslinking moieties.

Since Constancis is unrelated to mucoadhesive substances, first there would be no motivation for the combination proposed in the Official Action. One skilled in the art would not be motivated to change the polymers of Bernkop-Schnurch and add thiol groups based on the disclosure of Constancis. The principle of binding of bioadhesives is based, according to

Constancis, on a diffusion process of the monomers/oligomers into the tissue followed by a stabilizing polymerization process via oxidation of the thiol groups. This is similar to the principle used in other "super glues," such as glues based on cyanoacrylates which diffuse into surfaces and subsequently polymerize. The goal for bioadhesion is to achieve a very tight and strong connection of the bioadhesive with a given cell or tissue surface or to achieve a strong connection between cell or tissue surfaces. The "goal" for the compounds of Constancis is thus to adhere directly to the tissue.

By contrast, "mucoadhesion," as in Bernkop-Schnurch and the instant invention, is based on a different scientific concept. Mucus is a loosened, extremely wide meshed network which is characteristic for the mucus layers. A tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is, therefore, neither necessary nor desired for a mucoadhesive polymer. A covalent binding of the mucoadhesive polymer directly to the tissue surface could have extremely negative effects. For example, a covalent binding of a perorally administered drug to the epithelial cells of the gastrointestinal tract would lead to an obstruction of bowels. Mucoadhesive polymers thus should specifically bind to the mucus layer above the tissue in these areas. With a mucus turnover of about 6-8 hours, the above-described effect (e.g., obstruction of bowels) is prevented by covalently linking the mucoadhesive polymers to the mucus rather than the tissue itself. Please note Figure 1 from Muller and Hildebrand, "Pharmazeutische Technologie: Moderne Arzneiformen," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart (1997), Stuttgart, Germany, p. 280, which illustrates the adhesion of a mucoadhesive polymer to the mucus gel layer.

The compounds used by Constancis may be used *in vitro* or *in vivo* for binding biological tissues to each other or for binding a biological tissue and, e.g., an implanted biomaterial. The mucoadhesive polymers are intended to bind to the mucus gel layer and not to a tissue. This object of the bioadhesives as in Constancis is thus completely different from the object of mucoadhesive polymers, as described for applicants invention in the instant specification. *See, e.g.*, page 2, first paragraph. Thus, there would have been no motivation for one skilled in the art to combine the cited art of Bernkop-Schnurch and Constancis as proposed in the Official Action.

As recognized by the Federal Circuit, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself. In re Oetiker, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992). In establishing a *prima facie* case of obviousness under 35 U.S.C. 103, it is incumbent upon the examiner to provide a reason *why* one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. Ex parte Nesbit, 25 USPQ2d 1817, 1819 (BPAI 1992). As stated above, in the present case, no such motivation exists.

The binding of the mucoadhesive polymers as claimed is based on a completely different and novel mechanism for mucoadhesion. Applicants' invention is based on the observation that the mucus consists of mucus glycoproteins, which are connected with each other via numerous disulfide bonds. By the addition of a thiolated mucoadhesive polymer, new disulfide bonds are formed via thiol/disulfide exchange reactions between the polymer and

the mucus glycoproteins. This mechanism is illustrated in the enclosed Figure 2. This mechanism has previously never been proposed or reported in the field of mucoadhesive polymers. As noted by the Examiner, Bernkop-Schnurch do not disclose or suggest thiol-group containing polymers. As Constancis is unrelated to mucoadhesive polymers, this mechanism also is not disclosed or suggested in this reference.

Prior to the instant invention, the formation of secondary bond formation was regarded as the principle source of mucoadhesion. *See, e.g.*, Hunt et al, "Mucoadhesive Polymers in Drug Delivery Systems," in Drug Delivery Systems, Ellis Horwood, New York). That carboxyl groups in their non-ionized form are capable of strong hydrogen bond formation was regarded as a substantial reason for the mucoadhesive properties of such substances. *See*, Hunt, p. 186, third paragraph, which states:

In accordance with the theory that secondary bond formation is the principal source of mucoadhesion, those polymers with carboxyl groups present are all, without exception, mucoadhesive. The carboxyl group in its unionized form is capable of strong H-bond formation, and in its ionized form also able to interact electrostatically. However, the functional groups on the polymer backbone should not be in such close proximity that they interfere with each other (e.g. by intramolecular H-bonding). As the carboxyl concentration along a polymer chain decreases, for example, in moving from sodium alginate to Karya gum to gelatin, the mucoadhesive strength also decreases.

With respect to mucoadhesion, it is further stated that the direct interaction with the tissue or membrane surface is, in contrast with bioadhesion, not of relevance for mucoadhesion. *See, e.g.*, Hunt, p. 184, second paragraph, last sentence.

It should further be noted that none of the mucoadhesive polymers known in the art prior to the instant invention, as evidenced by Hunt, Table 1 and Figure 1, contained any thiol groups. This evidences that the role of thiol groups in the process of mucoadhesion was neither known nor proposed prior to applicants' invention. Even in mucoadhesive polymers

based on proteins, no free thiol groups are present (such polymers would also have more than 10 different monomers). *See, e.g.*, Hunt, page 190, wherein the amino acid composition of gelatine is listed and cysteine residues are not even listed under amino acids with "low abundance."

Figure 1 of Hunt makes clear that the compounds regarded as the most potent mucoadhesive polymers in the prior art did not contain any thiol groups, much less "at least one non-terminal thiol group" as instantly claimed. It was thus surprising to applicants that by providing non-terminal thiol groups in such mucoadhesive polymers, the mucoadhesive properties of such polymers could be enormously improved. Indeed, the thiolated mucoadhesive polymers of the instant invention have mucoadhesion properties that are significantly superior to the best mucoadhesive polymers known in the art.

Therefore, even if Constancis taught polymers having non-terminal thiol groups, there would have been no motivation for one skilled in the art to incorporate thiol groups into mucoadhesive polymers to achieve the instant invention.

Moreover, even if the cited art were combined, the instant invention would not be achieved. The combination of Bernkop-Schnurch and Constancis would not provide mucoadhesive polymers having "at least one non-terminal thiol group" as claimed by applicants. Neither Bernkop-Schnurch nor Constancis teach polymers having non-terminal thiol groups.

In view of the above, withdrawal of the rejection of record under §103(a) is thus respectfully requested and believed to be in order.

Further and favorable action in the form of a Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this amendment or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution may be expedited.

Respectfully submitted,

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**Attachment to Reply and Amendment dated December 21, 2001**

**Marked-up Claims 48, 50, 53-55, 71, 72, 87 and 89-91**

48. (Amended) A method of enhancing permeation of active substances through mucosa in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition comprising a mucoadhesive polymer having not more than 10 different monomers and at least one non-terminal thiol group in an amount effective for enhancing permeation of active substances, and at least one active substance capable of being taken up via a mucosa in a therapeutically effective amount.

50. (Amended) A method of enhancing permeation of active substances through mucosa in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition comprising

a mucoadhesive polymer having not more than 10 different monomers and at least one non-terminal thiol group in an amount effective for enhancing permeation of active substances, wherein said mucoadhesive polymer is selected from the group consisting of a thiolated copolymer of acrylic acid and divinyl glycol, thiolated chitosan, thiolated sodium carboxymethylcellulose, thiolated sodium alginate, thiolated sodium hydroxypropylcellulose, thiolated hyaluronic acid, thiolated pectin and derivatives of these thiolated polymers, and

at least one active substance capable of being taken up via a mucosa in a therapeutically effective amount.

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53. (Amended) A method of [treating] administering an active ingredient to an individual in need thereof [of a treatment] wherein the active ingredient is taken up via mucosae, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition comprising a mucoadhesive polymer having not more than 10 different monomers and at least one non-terminal thiol group in an amount effective to introduce an active substance to said mucosae and at least one active substance to be taken up via mucosae in a therapeutically effective amount, wherein said active ingredient is capable of adhering to a mucosa selected from the group consisting of intradermal, intraocular and intraarticular mucosa.

54. (Amended) A method of inhibiting enzymes in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition which comprises a mucoadhesive polymer having not more than 10 different monomers and at least one non-terminal thiol group, and at least one active substance capable of inhibiting enzymes in an amount effective for inhibiting said enzymes.

55. (Amended) A method of inhibiting zinc ion-dependent enzymes in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition which comprises a mucoadhesive polymer having not more than 10 different monomers and at least one non-terminal thiol group, and at least one active

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substance capable of inhibiting zinc ion-dependent enzymes in an amount effective for inhibiting said enzymes.

71. (Amended) A method as set forth in claim 53, wherein said [drug] pharmaceutical composition further comprises at least one active substance to be taken up via said mucosa.

72. (Amended) A polymer as set [form] forth in claim 30, wherein said derivatives are selected from the group consisting of derivatives obtained by auto-cross-linking, introduction of functional groups, attachment of complexing agents and coupling of enzyme inhibitors.

87. (Amended) A method of enhancing permeation of active substances through mucosa in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition according to claim 82.

89. (Amended) A method of [treating] administering an active ingredient to an individual in need of [a treatment] an active ingredient which will adhere to a mucosa layer, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition according to claim 82, wherein said pharmaceutical

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composition adheres to a mucosa layer selected from the group consisting of intradermal, intraocular and intraarticular mucosa.

90. (Amended) A method of inhibiting enzymes in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition according to claim 82, wherein said active substance is capable of inhibiting enzymes, in an amount effective to inhibit said enzymes.

91. (Amended) A method of inhibiting zinc ion-dependent enzymes in an individual, said method comprising administering to said individual [an effective amount of] a pharmaceutical composition according to claim 82, wherein said active substance is capable of inhibiting zinc ion-dependent enzymes, in an amount effective to inhibit said enzymes.